Tumor immunity

Lecture 16

By

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Introduction

- **Cancer** is a major health problem worldwide and one of the most important causes of morbidity and mortality in children and adults.
- The lethality of malignant tumors is due to their **uncontrolled growth within normal tissues**, causing damage and functional impairment.
- The malignant phenotype of cancers reflects:

1. defects in regulation of cell proliferation,
2. resistance of the tumor cells to apoptotic death,
3. ability of the tumor cells to invade host tissues and metastasize to distant sites,
4. tumor evasion of host immune defense mechanisms.

- The existence of immune surveillance has been demonstrated by the increased incidence of some types of tumors in immunocompromised experimental animals and humans.

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- It is now clear that **the innate and adaptive immune systems do react against many tumors**, and exploiting these reactions to specifically destroy tumors remains an important goal of tumor immunologists.
- Several characteristics of tumor antigens and immune responses to tumors are fundamental to an understanding of tumor immunity and for the development of strategies for **cancer immunotherapy**.
- **When a cell undergoes malignant transformation, it acquires new surface antigens**.
- It may **lose some normal antigens** and this makes a tumor antigenically different from the normal tissues of the host.
- A tumor can, therefore, be considered an **allograft** and be expected to induce an immune response.

Tumor antigen

- **Tumor antigens** are antigens that are present in malignant cells but absent in the normal cell of the host.
- Two types of tumor antigens have been identified on tumor cells:
- 1. Tumor-specific transplantation antigens (TSTAs)
- 2. Tumor-associated transplantation antigens (TA- TAs).
- **1. Tumor-specific transplantation antigens (TSTAs):**
- unique to tumor cells and do not occur on normal cells.
- identified on tumors induced with chemical or physical carcinogens and on some virally induced tumors.
- Different carcinogen produce different TSTA
- In contrast, **one virus will possess the same antigen** TSTA

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- **2. Tumor-associated transplantation antigens (TATAs):**
- **TATA present on tumor cells (higher level)** and also on some normal cells **(low levels)**,
- Detection of TATA use for diagnosis of certain tumors and antibodies raised against them can be useful for immunotherapy.
- The more common tumor-associated antigens are **oncofetal antigens** and increased levels of normal oncogene products. TATAs fall into three categories:
- i.**Tumor-associated carbohydrate antigens (TACAs)**:
- abnormal forms of widely expressed **glycoproteins and glycolipids** such as **mucin-associated antigen** detected in **pancreatic and breast cancers**.
- ii. **Oncofetal tumor antigens**:
- Oncofetal tumor antigens, appear early in embryonic development, If these antigens appear later on cancer cells, they are recognized as nonself and induce an immunologic response. Two well-studied oncofetal antigens are **alpha fetoprotein (AFP) in hepatoma and carcinoembryonic antigen (CEA)** found in **colonic cancer**.
- iii. **Differentiation antigens**:
- **CD10,** an antigen expressed in early B lymphocytes, is present in B cell leukemias. Similarly, **prostate specific antigen (PSA)** is expressed on the normal as well as cancerous prostatic epithelium. Both serve as useful differentiation markers in the diagnosis of lymphoid and prostatic cancer

Type of Antigen	Examples of Human Tumor Antigens
Products of mutated oncogenes, tumor suppressor genes	Oncogene products: Ras mutations (~10% of human carcinomas), p210 product of Bcr/Abl rearrangements; (CML) Tumor suppressor gene products: mutated p53 (present in ~50% of human tumors)
Unmutated but overexpressed products of oncogenes	HER2/Neu (breast and other carcinomas)
Mutated forms of cellular genes not involved in tumorigenesis	Various mutated proteins in melanomas recognized by CTLs
Products of genes that are silent in most normal tissues	Cancer/testis antigens expressed in melanomas and many carcinomas; normally expressed mainly in the testis and placenta
Normal no oncogenic proteins overexpressed in tumor cells	Tyrosinase, gp100, MART in melanomas (normally expressed in melanocytes)
Products of oncogenic viruses	Papillomavirus E6 and E7 proteins (cervical carcinomas) EBNA-1 protein of EBV (EBV-associated lymphomas, nasopharyngeal carcinoma)
Oncofetal antigens	Carcinoembryonic antigen on many tumors, also expressed in liver and other tissues during inflammation a-Fetoprotein
Glycolipids and glycoproteins	GM2, GD2 on melanomas
Differentiation antigens normally present in tissue of origin	Prostate-specific antigen in prostate carcinomas CD20 on B cell lymphomas

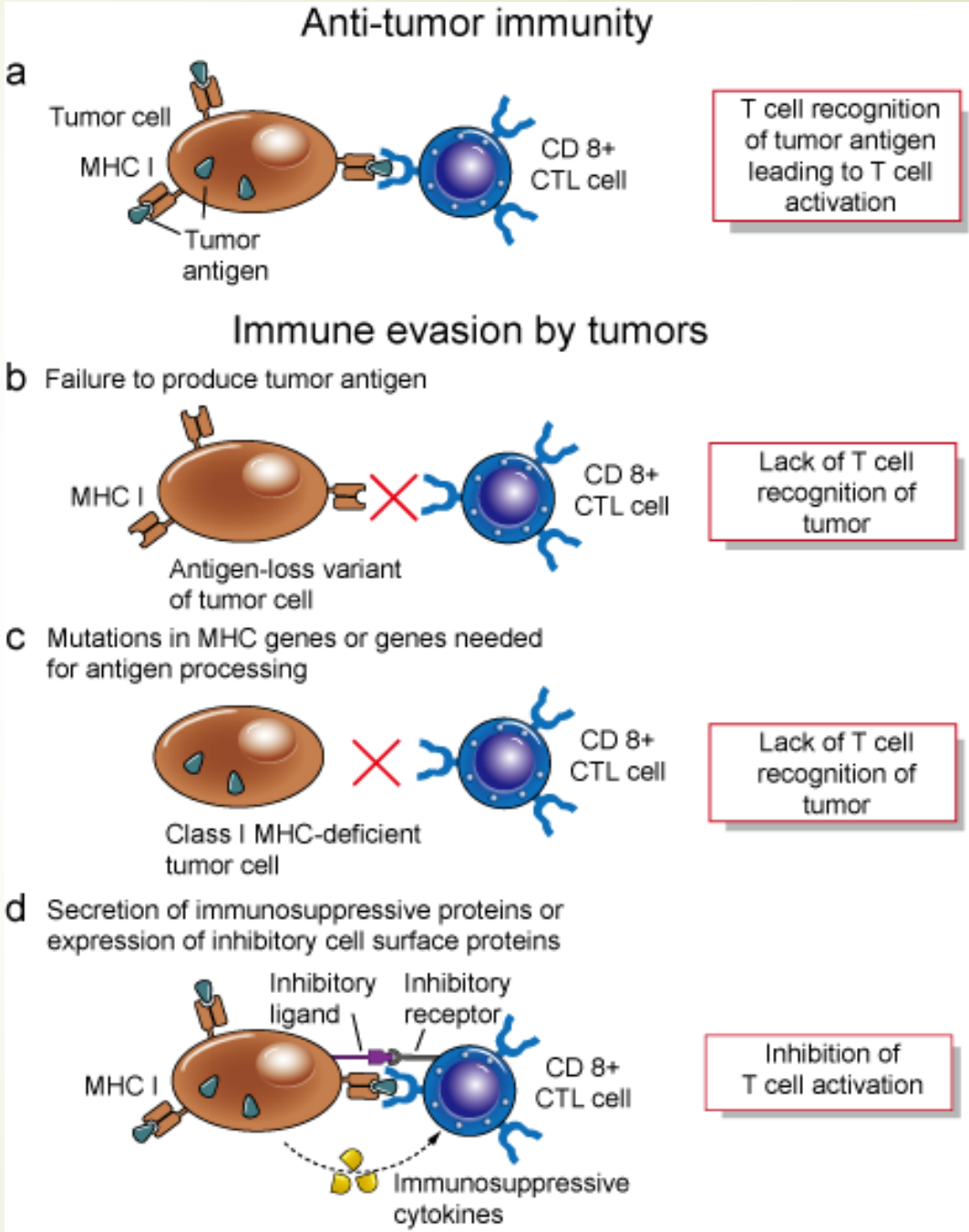
Immune Responses to Tumors

1. T Lymphocytes
tumor cells killed by CD8+ CTLs. CD4+ cells providing cytokines for differentiation of naive CD8+ T cells into effector and memory CTLs. Cytokine TNF and IFN-γ can increase tumor cell class I MHC expression and sensitivity to lysis by CTLs.

2. Antibody
antibodies produced against various tumor antigens. Antibodies may kill tumor cells by activating complement or by antibody-dependent cell-mediated cytotoxicity.

3. Natural Killer Cell
NK cells are lymphocytes that are capable of destroying tumor cells without prior sensitization, so it provide the **first line of defense against many tumors.**

4. Macrophages
Macrophages recognize of damage-associated molecular patterns from dying tumor cells by macrophage TLRs and activated IFN-γ produced by tumor-specific T cells.



Immunological surveillance

- tumor cells must develop mechanisms to escape or evade the immune system in immunocompetent hosts. Several such mechanisms may be operative:
- 1. **Weak immunogenicity**: Some tumors do not elicit an immune response. But when their numbers increase enough to provoke immune response the tumor load may be too great for the host's immune system to mount an effective response.
- **2. Modulation of surface antigens**: Certain tumor specific antigens disappear from the surface of tumor cells in the presence of serum antibody and then to appear after the antibody is no longer present.
- **3. Masking tumor antigens**: Certain cancers produce copious amounts of a mucoprotein called sialomucin. It binds to the surface of the tumor cells. Immune system does not recognize these tumor cells as foreign since sialomucin is a normal component.

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- **4. Induction of immune tolerance:** Some tumor cells can synthesize various immunosuppressants. They may also activate specific Ts cells. Both these suppress the effector T and B cell clones.
- **5. Production of blocking antibodies:** Antitumor antibody itself acts as a blocking factor. The antibody, binds to tumor-specific antigens and masks the antigens from cytotoxic T cells. Some tumor cells invoke immune system to produce blocking antibodies that cannot fix and activate complement, so lysis of tumor cell is not possible. Blocking antibodies also cover the surface of cancer cells, preventing Tc cells from binding to hidden receptors.
- **6. Low levels of HLA class I molecules:** In some instances, tumor cells express reduced levels of HLA class I molecules. This impairs presentation of antigenic peptides to cytotoxic T cells.

Immunotherapy of cancer

- Different approaches have been attempted in the immunotherapy of cancer—active or passive, specific or nonspecific.
- **Nonspecific Active Immunotherapy**
- Biological response modifiers (BRMs) are used to enhance immune responses to tumors and fall into four
- major groups:
- **(i) Bacterial products; ---**BCG is effective against bladder tumors.
- **(ii) Synthetic molecules; -----**Dinitrochlorobenzene has been tried in the treatment of squamous and basal cell carcinoma of the skin.
- **(iii) Cytokines; ------**Immunotherapy with cytokine can
- cause tumor regression.
- **(iv) Hormones:-----**thymic hormones can be used to enhance T cell
- function.
- **Specific Passive Immunotherapy**
- **i. Nonspecific (lymphokine-activated killer (LAK) cells)**
- **ii. Specific** (antibodies alone or coupled to drugs, prodrugs, toxins or radioisotope, bispecific antibodies T cells)
- **iii. Combined** (LAK cells and bispecific antibody)

Thank you